

## SERTRALINE-ASSOCIATED INTERSTITIAL LUNG DISEASE: A CASE SERIES AND LITERATURE REVIEW

*Shimon Izhakian<sup>1,2\*</sup>, Dror Rosengarten,<sup>1,2\*</sup> Barak Pertzov<sup>1,2</sup>, Ahuva Grubstein<sup>2,3</sup>, Moshe Heching<sup>1,2</sup>, Ludmila Fridel<sup>3,4</sup>, Mordechai R. Kramer<sup>1,2</sup>*

<sup>1</sup>Pulmonary Institute, Rabin Medical Center, Petah Tikva, Israel; <sup>2</sup>Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel; <sup>3</sup>Mammography Clinic, Department of Radiology, Rabin Medical Center, Petah Tikva, Israel; <sup>4</sup>Pathology Institute, Rabin Medical Center, Petah Tikva, Israel; \*Equal contribution

**ABSTRACT.** Sertraline-associated interstitial lung disease (ILD) is a rare entity. A search of the English medical literature retrieved only 9 such cases. We report herein on an additional 12 patients who developed ILD during treatment with sertraline. The patients met the criteria for drug-induced pulmonary toxicity such as exposure to drug, correlation of the drug with clinical symptoms, lung imaging, lung biopsy findings, exclusion of other potential causes and improvement after drug removal. We review the available data and discuss various aspects of this entity. The possibility of drug-induced ILD should be considered in an individual who during treatment with sertraline develops dyspnea, cough, and radiographic findings compatible with ILD. Further epidemiological studies should be conducted to explore the association of sertraline treatment with ILD, and to delineate, substantiate, and broaden our knowledge of this rare entity.

**KEY WORDS:** Interstitial lung disease, Pulmonary fibrosis, Sertraline, SSRI

### INTRODUCTION

Over 350 medications have been associated with interstitial lung disease (ILD) (1-4). Nonetheless, the diagnosis of drug-induced ILD is challenging due to the often non-specific clinical and radiological findings that may mimic virtually any pulmonary syndrome (1, 2). In some patients with this pathology, a clear temporal relationship is apparent between the introduction of the drug and the onset of symptoms. However, the most common scenario is a delay in establishing an

association between disease and medication, and this can result in a fatal event (1, 2).

Eleven percent of the American population above age 11-years is estimated to be treated with antidepressant medications (5). Among these, selective serotonin reuptake inhibitors (SSRIs) are frequently used as first-line antidepressants because of their efficacy, tolerability, and general safety in overdose. In addition, SSRIs potentially treat anxiety, which is often concomitant with depressive syndromes. With these advantages, sertraline has been one of the most popular SSRIs, since its introduction into the market in 1991. Despite the enormous level of exposure in the population, sertraline-associated ILD has only rarely been reported in the English medical literature (6-13).

We herein present a description of one patient, and report on an additional 11 patients with sertraline-associated ILD. We also review the relevant literature, discuss various aspects of this

Received: 18 February 2021

Accepted after revision: 26 April 2021

Correspondence: Shimon Izhakian, MD, PhD,  
Pulmonary Institute, Rabin Medical Center,  
Beilinson Hospital, Jabotinski St. 39, Petah Tikva 49100, Israel.  
E-mail: shimixyz@gmail.com

entity, and attempt to define the clinical profile of the affected patients; this may facilitate recognizing the development of ILD during treatment with sertraline.

### CLINICAL CASE 1

A 27-year-old woman presented to her primary care physician with a one-month history of dyspnea attacks. She described feeling shortness of breath in rest that lasted a few minutes every week in the last month. The patient had no previous diseases, never smoked, and took only birth control pills (desogestrel/ethinyl estradiol) as regular medications. She worked as a secretary at a clothing store. There was no history of recent travel, use of illicit drugs, alcohol drinking, or exposure to toxic substances.

The patient was afebrile, with a pulse 80/min and regular, blood pressure 121/81 mm Hg, respiratory rate 15 breaths/min, and oxygen saturation 97% while she was breathing ambient air. A physical examination was unremarkable and a basic laboratory evaluation was normal. Chest radiography, electrocardiography, echocardiography, and ergometry were normal. High resolution computed tomography (HRCT) of the chest was unrevealing (Figure 1a). The patient was examined by a pulmonologist who found no pathological findings on physical examination and spirometry. He prescribed fluticasone/vilanterol inhaler for suspected bronchial asthma. Three months after the first symptoms, the patient was referred to a psychiatrist due to continuation of her symptoms. The psychiatrist was impressed by a generalized anxiety and prescribed sertraline at a dosage of 100 mg/day.

One month after sertraline initiation, the woman was referred to the emergency department with worsening dyspnea. Her vital signs were temperature 36.4°C, regular pulse 100/min, blood pressure 101/57 mm Hg, and oxygen saturation 94% at ambient air. Complete blood count, blood gases, routine biochemical panel, and level of D-dimer were normal. Chest X-ray revealed small pneumomediastinum. Chest HRCT showed small pneumomediastinum and diffuse ground-glass opacities (Figure 1b). The patient was discharged home with an antibiotic course and was referred to an ambulatory pulmonary evaluation.

The patient underwent bronchoscopy with bronchoalveolar lavage that revealed marked lymphocytosis with CD4/CD8 ratio <1, and sterile cultures for bacteria and fungi. Serologic investigation for autoimmune disease revealed normal finding including antinuclear antibody, anti-double stranded DNA, anti-proteinase, anti-myeloperoxidase, anti-JO-1, anti-SCL-70, anti-centromere, anti-RNP, anti-Ro, anti-La and anti-Smith antibodies, complement C3 and C4, serum immunoglobulins, and serum protein electrophoresis. The clinical picture was summarized by the pulmonologist as ILD or hypersensitivity pneumonitis of unknown cause. The patient was hospitalized and treated with pulse therapy (intravenous methylprednisolone at a dosage of 500 mg once daily for 3 consecutive days), and was then discharged with treatment by prednisone 40 mg daily following tapering by 10 mg every 10 days.

Two months after sertraline initiation, the woman again presented to the emergency department, due to continued deterioration in her respiratory condition. Her medical history revealed that her psychiatrist had increased the sertraline dosage to 200 mg/day. On clinical examination, pneumothorax was diagnosed and treated with chest tube insertion and the patient was subsequently admitted to the department of thoracic surgery. Six days later, the chest tube was removed but the respiratory failure worsened. Clinical examination revealed worsening opacities, signs of fibrotic changes, and pleural effusion on chest HRCT (Figure 1c). Despite treatment with broad-spectrum antibiotics and corticosteroids, the patient's clinical condition deteriorated significantly, until she required mechanical ventilation and admission to the intensive care unit. At this time point, treatment with sertraline was discontinued. Due to severe respiratory failure, the patient was connected to an extracorporeal membrane oxygenation (ECMO) machine for 17 days. Corticosteroid dosage was increased to pulse therapy. She also had a brain hemorrhage and underwent a successful decompressive craniectomy. Surgical wedge lung biopsy was evaluated by three pathological centers revealed findings consistent with non-specific interstitial pneumonia with interstitial homogenous inflammation and mild fibrosis.

One month from the beginning of the current hospitalization, the patient was weaned from mechanical ventilation and transferred to a

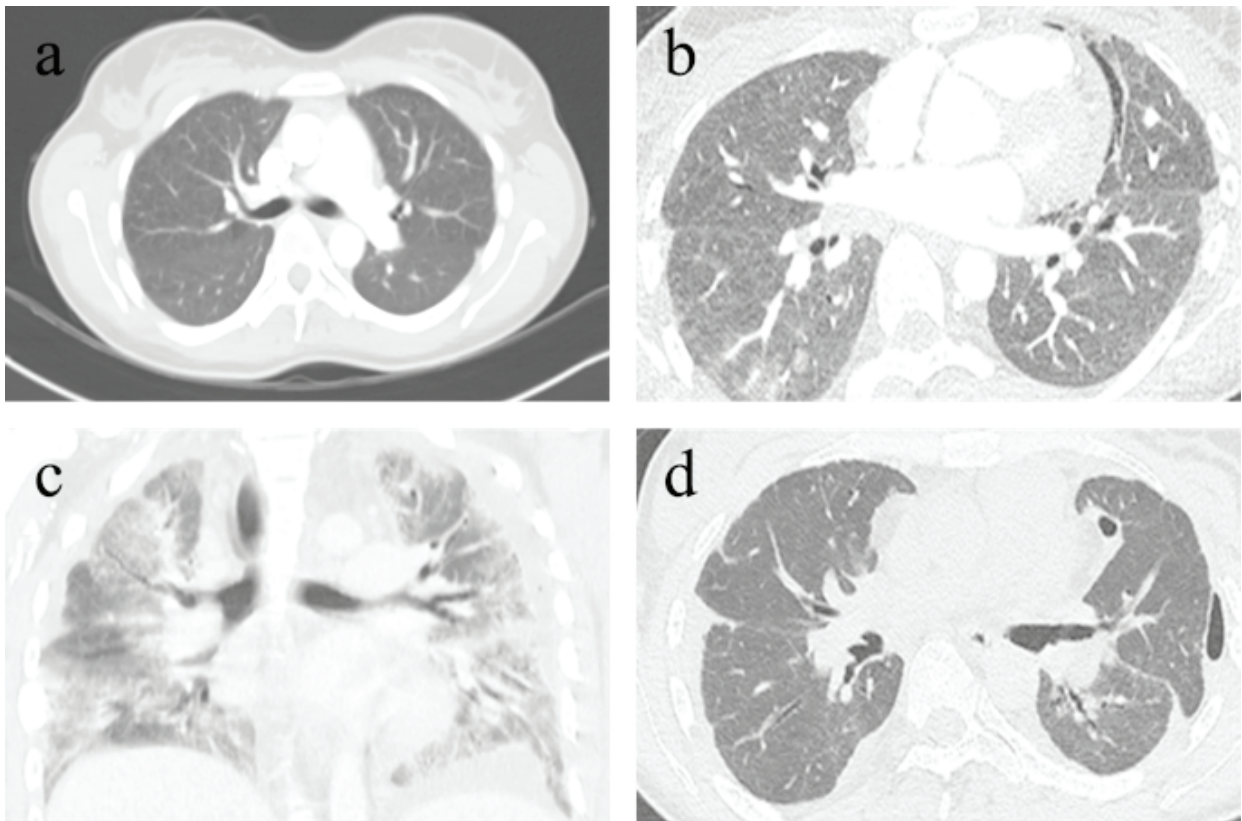
neurological rehabilitation facility, where she was treated with prednisone and mycophenolate mofetil. Six months after discharge from the hospital, the patient was weaned from oxygen. A chest HRCT scan revealed significant improvement, with almost complete resolution of pulmonary opacities (Figure 1d). One year follow up after discharge did not reveal clues for autoimmune disease by anamnesis, physical examination, and repeated autoimmune laboratory.

#### CASES 2-12 AND REVIEW OF THE LITERATURE

We report on 11 additional patients who developed sertraline-associated ILD. The demographic and clinical data of these 12 patients are detailed in Table 1. The range of age of the patients was 27-85 years; eight were females. The records of each patient were examined to rule out possible alternative

diagnoses, such as pulmonary infection, heart failure, acute lung injury related to fumes/toxins, rheumatologic disease, pneumoconiosis, vasculitis and malignancy. Sertraline-associated ILD demonstrated a variety of clinicopathologic patterns: pulmonary fibrosis (n=6), non-specific interstitial pneumonia (n=5), and organizing pneumonia (n=1). The outcomes were: recovery (n=3), improvement (n=1), stabilization (n=4), and deterioration (n=2) or death (n=2).

Reviewing the literature, we retrieved reports of only nine other persons affected by sertraline (6-13). The detailed demographic and clinical data of these patients are presented in Table 2. Summarizing the data for a total of 21 patients with sertraline-associated ILD, including our patients and those presented in previous reports (Tables 1 and 2), the median age was 57 years (range 27-85); 57% were females and



**Figure 1.** Chest computed tomography of a 27-year old woman with sertraline-associated interstitial lung disease (patient 1 on Table 1), over the course of time. a Two months after onset of symptoms. b One month later – small pneumothorax and diffuse ground-glass opacities. c Two months later – worsening opacities with signs of fibrotic changes, traction bronchiectasis, bilateral pleural effusion, and post-pneumothorax drainage. d Six months later – significant improvement, with almost complete resolution of pulmonary opacities.

**Table 1.** Characteristics of our 12 patients with sertraline-associated interstitial lung disease.

Case no.	Age/Sex	Smoker	Duration of using sertraline	Other medications	Comorbidities	Symptoms	Presentation	Clinicopathologic diagnosis	Outcome after drug discontinuation	Treatment
1	27/F	No	3 months	Desogestrel/ethinyl estradiol and fluticasone/vilanterol	Allergic rhinitis	Dyspnea	Subacute progressive (2 months)	Interstitial fibrosis with non-specific interstitial pneumonia	Recovery	Mycophenolate and prednisone
2	52/F	Yes	1 year	No	Depression and obesity	Cough	Chronic (5 years)	Non-specific interstitial pneumonia	Recovery	Mycophenolate and prednisone
3	68/M	Yes	6 months	Valsartan, amlodipine and hydrochlorothiazide	Hypertension, GERD and scoliosis	Dyspnea	Chronic (3 months)	Organizing pneumonia	Deterioration	Prednisone and nintedanib
4	52/F	No	1 year	NR	Hypertension and allergic rhinitis	Cough	NR	Non-specific interstitial pneumonia	Recovery	Prednisone
5	67/M	Yes	8 years	Atenolol, clopidogrel, omeprazole, and simvastatin	Ischemic heart disease and GERD	Dyspnea	Chronic (2 years)	Pulmonary fibrosis	Death	Prednisone and pirfenidone
6	68/F	No	3 years	Pantoprazole	Hypertension, depression and GERD	Dyspnea	NR	Non-specific interstitial pneumonia	Stabilization	Mycophenolate and prednisone
7	72/M	Yes	2 years	Ramipril, bisoprolol, rivaroxaban, and simvastatin	Hypertension and atrial fibrillation	Dyspnea	Chronic (1 year)	Pulmonary fibrosis and emphysema	Stabilization	Supportive
8	57/F	No	2 years	Atenolol	Hypertension and depression	Dyspnea	Chronic (3 years)	Non-specific interstitial pneumonia	No discontinuation	Prednisone and azathioprine
9	72/M	No	NR	Esomeprazole	GERD	Cough	Chronic (2 years)	Pulmonary fibrosis	Improvement	No
10	85/F	No	1 year	Bisoprolol, famotidine, and nitrofurantoin	Hypertension, anxiety, and recurrent UTI	Cough and dyspnea	Chronic (2 years)	Pulmonary fibrosis	Deterioration	Prednisone
11	81/F	Yes	NR	Losartan, amlodipine, and alprazolam	Hypertension and obesity	Dyspnea	NR	Pulmonary fibrosis	Stabilization	No
12	70/F	Yes	NR	Gabapentin and metformin	Obesity and diabetes mellitus	Dyspnea	NR	Pulmonary fibrosis	Stabilization	Nintedanib

Abbreviations: ILD: interstitial lung disease; F; female; M: male; NR: non-reported; GERD: gastroesophageal reflux disease; UTI: urinary tract infection.

**Table 2.** Characteristics of nine patients with sertraline-associated interstitial lung disease reported in the English medical literature

Reference, no./author/year	Age/Sex	Smoker	Duration of using sertraline	Other medications	Comorbidities	Symptoms	Presentation	Clinicopathologic diagnosis	Outcome after drug discontinuation	Treatment
[4] Barnés et al. 1999	40/F	No	7 days	Clomipramine and alprazolam	Depression and anxiety	Dyspnea, fever, and cough	Acute (4 days)	Acute eosinophilic pneumonia	Recovery	Supportive
[5] Savici and Katzenstein 2001	43/M	NR	NR	Methadone, lansoprazole	GERD	Fever and dyspnea	Chronic (11 months)	Diffuse alveolar damage	NR	NR
[5] Savici and Katzenstein 2001	55/F	NR	NR	Methadone, gabapentin, and alprazolam	Depression, anxiety, and GERD	Fever and dyspnea	Chronic (11 months)	Diffuse alveolar damage	NR	NR
[6] Thornton et al. 2009	33/M	Yes	3 years	Risperidone	Schizophrenia	Cough and dyspnea	Chronic (6 months)	Predominant non-specific interstitial pneumonia	Improvement	Cyclophosphamide, methylprednisolone and azathioprine
[7] Torok et al. 2012	52/M	Yes	6 months	No	Depression	Cough and dyspnea	Subacute (1 month)	Diffuse alveolar damage	Recovery	Methylprednisolone
[8] Rosenberg et al. 2017	85/M	Yes	7 years	NR	Depression	Fatigue and cough	Chronic (35 months)	NR	No discontinuation	NR
[9] Muftah et al. 2018	49/F	No	6 months	Lisinopril	Hypertension, anxiety, and depression	Dyspnea, myalgia, and cough	Acute (4 days)	Acute eosinophilic pneumonia	Recovery	Prednisone
[10] Virdee et al 2019	47/F	No	9 months	Lansoprazole	Depression GERD	Dyspnea, pleuritic pain	Acute or chronic	NR	Recovery	Antibiotics and methylprednisolone
[11] Trangu et al 2020	63/M	No	Several years	No	Depression	Daily fever and cough,	Acute (10 days)	Organizing pneumonia	Recovery	Antibiotics and methylprednisolone

ILD interstitial lung disease, F female, M male, NR non-reported, GERD gastroesophageal reflux disease

43% smokers. The reported time of exposure to sertraline treatment varied from 7 days to 8 years. Most patients were prescribed additional medications and had comorbidities; the latter were predominantly depression, anxiety, hypertension, and gastroesophageal reflux disease. The most common presenting symptoms were dyspnea and cough. Clinical presentation of sertraline-associated ILD may be acute, subacute, and chronic. A chronic course of the disease presented more often, while five patients demonstrated acute or subacute onset. Sertraline-associated ILD demonstrated a variety of clinicopathologic patterns: pulmonary fibrosis (n=7), non-specific interstitial pneumonia (n=6), diffuse alveolar damage (n=3), acute eosinophilic pneumonia (n=2), organizing

pneumonia (n=2), and hypersensitivity pneumonitis (n=1). A lung biopsy was performed in 14 patients; the diagnosis was based on clinical and radiological (chest HRCT) findings in the remaining 7. Among the 21 patients with sertraline-associated ILD, 6 were treated with corticosteroids only, 5 with a combination of corticosteroids and cytotoxic agents, and 3 with antifibrotic medications. Treatment was not reported for 3 patients, and specific therapy was not administered to 4.

## DISCUSSION

We presented a case series of 12 patients with ILD associated with sertraline treatment; the largest



report published to date on this rare entity. In addition, we reviewed 9 other similar cases reported in the literature (6-13).

The underlying mechanisms of sertraline-induced ILD are not completely understood. The non-specific pathways involved include direct cytotoxic damage of pneumocytes or the alveolar capillary endothelium by oxidative stress, and an immune-mediated lung injury response (2, 10). The specific metabolic pathway of sertraline via cytochrome P450 enzymes has a role in the initiation and propagation of ILD. Several P450 enzymes are responsible for the metabolism of sertraline; the primary contribution is by CYP2D6, and lesser contributions by CYP2C19, CYP2B6, CYP3A4, and CYP2C9 (14). These enzymes have genetic polymorphisms due to duplications, gene insertions, base pair deletions, copy number variations, and single nucleotide polymorphisms. These polymorphisms underlie differences in enzyme activity that range from no enzyme activity (poor metabolizers), decreased activity (intermediate metabolizers), and normal (extensive metabolizers/wild type) to increased (ultra-rapid metabolizers) enzyme activity (14). A common consequence of these various phenotypes is therapeutic resistance or inefficacy due to insufficient plasma levels of the drugs that are metabolized by polymorphic rapid metabolizer phenotypes. Moreover, slow metabolism may lead to elevated plasma levels, resulting in pulmonary toxicity. Other possible pathophysiological mechanisms for sertraline-induced ILD include the specific effects of serotonin in immune cells. Serotonin plays an important role in immune modulation (15). The majority of immune cells express at least one serotonin receptor, and serotonin modulates cytokine secretion, recruitment, and phagocytic activity of neutrophils, and also activation of eosinophils, basophils, and lymphocytes (15). Notably, the use of other antidepressants with a metabolism similar to that of sertraline (SSRIs), such as venlafaxine and fluoxetine, has been reported to be associated with ILD (10, 16, 17).

The diagnosis of sertraline-associated ILD is challenging for several reasons. First, clinical, laboratory, radiographic, and histological findings of drug-induced ILD can be similar to ILD due to other causes. Second, patients often present at a late stage of the disease, which might add further difficulty to associate ILD with the prescribed drug. Third, ILD

symptoms mostly do not present immediately after initiating sertraline therapy, and the clinical condition may not improve immediately after discontinuation of the drug. Fourth, polypharmacy is not rare in the modern era, which could further hinder differentiating ILD that is associated with a given medication. In this case series, we tried to exclude causes other than sertraline. The patients met the criteria for drug-induced pulmonary toxicity (exposure to a drug, correlation of the drug with clinical/imaging/laboratory findings, exclusion of other potential causes, and improvement after drug removal) (2). However, some of our patients were treated with other drugs that can potentially cause ILD, such as nitrofurantoin, simvastatin, amlodipine, and hydrochlorothiazide. This poses a challenge to detecting the offending cause for ILD.

Prompt and accurate diagnosis of sertraline-associated ILD is important to ensure a favorable outcome. A firm diagnosis entails three key elements: high clinical suspicion, exclusion of other ILD causes, and possible clinical improvement following drug discontinuation. Bronchoalveolar lavage and lung biopsy are useful for the exclusion of alternative etiologies of ILD such as: infection, lymphangitic carcinomatosis, alveolar hemorrhage, and vasculitis (1, 2). Bronchoscopic lung cryobiopsy is preferred for patients with a low risk for complications. In contrast, for patients with a high risk for invasive procedures, the diagnosis may be established from typical clinical and chest HRCT findings. Notably, a definitive diagnosis of sertraline-induced ILD requires rechallenge by re-exposure to the drug (2). In one patient only, the diagnosis was confirmed by a drug provocation test as follows: improvement of diffuse alveolar damage after discontinuation of sertraline treatment, rechallenge of the medication with consequent exacerbation of ILD, and recovery after repeated discontinuation of sertraline (9). However, a drug provocation test for patients with ILD is generally considered unethical, due to an increased risk of irreversible pulmonary damage, and is recommended only for patients with mild ILD (2).

Treatment of sertraline-associated ILD depends on clinicopathologic features. Patients with inflammatory radiologic (ground-glass opacities and consolidation) and pathologic (cellular non-specific interstitial, organizing, and eosinophilic pneumonia) features should be treated with corticosteroids

alone or in combination with a cytotoxic agent (2). In contrast, patients with fibrotic radiologic (peripheral reticulation, traction bronchiectasis, and honeycombing) and pathologic (fibrotic non-specific and usual interstitial pneumonia) findings, anti-fibrotic therapy is indicated (18). However, the mainstay treatment of sertraline-associated ILD is discontinuation of the offending medication. Knowledge of the adverse effects of sertraline is very important, especially of pulmonary toxicity, which may be acute/subacute or chronic. Early recognition and withdrawal of the drug is vital. Indeed, for the 21 patients reviewed here, poor outcomes were associated with chronic presentation of sertraline-associated ILD, and prolonged periods of treatment with sertraline, ranging from 6 months to 8 years. Discontinuation of sertraline treatment was not reported in two patients, and in one patient the drug was not discontinued. Among the 18 patients who discontinued treatment with sertraline, the outcomes were mostly favorable: recovery (n=8), improvement (n=2), and stabilization (n=4). Deterioration or death was reported for four.

## Conclusions

The possibility of drug-induced ILD should be considered in a patient who during treatment with sertraline develops dyspnea, cough, and clinicopathologic findings compatible with ILD. Further, epidemiological studies should be conducted to explore the association of sertraline treatment with ILD, and to delineate, substantiate, and broaden our knowledge of this rare entity. Moreover, personalized medicine is moving toward optimizing treatment with sertraline. The role of introducing genetic screening (pharmacogenomics) prior to prescribing sertraline, and therapeutic drug monitoring for prevention of ILD should be investigated.

**Conflicts of Interest:** The authors declare no conflicts of interest on this study.

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